REMARKS

In the Claims:

Claims 25-26 are canceled herein without disclaimer or prejudice to pursuing the inventions of claims 25-26 in a continuing application. Claim 33 is amended herein such that it no longer depends from canceled claim 25 but now depends from pending claim 27. No new matter is added by this amendment. Thus, claims 27-34 are currently pending.

In the Specification:

35 U.S.C. § 102

Claims 25-34 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Botstein *et al.*, WO 99/35170, and claims 22-27, 31, 33, and 34 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Holtzman, WO 99/54343.

In the Amendment and Request for Reconsideration submitted December 21, 2004, Applicants argued that the submitted inventor declarations overcame the cited references. The Examiner has considered these declarations but the Office action states that the declarations are ineffective because those submitted December 21, 2004 were unsigned. The Examiner kindly notes that upon submission of signed declarations these rejections will be withdrawn. Applicants have herein attached, as Exhibit 1, signed copies of the declarations initially submitted December 21, 2004. Therefore, Applicants have overcome this ground of rejection and respectfully request that it be withdrawn.

35 U.S.C. § 101

Claims 25-34 remain rejected under 35 U.S.C. § 101 as allegedly not being supported by either a substantial asserted utility or a well established utility.

Applicants respectfully disagree with this ground of rejection. As previously argued, at pages 119 and 137 of the specification, Applicants assert a diagnostic utility for the claimed polypeptide. This assertion creates a presumption of utility sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 183 USPQ 288, 297 (CCPA 1974). *See also In re Jolles*, 206 USPQ 885 (CCPA 1980); *In re Irons*, 144 USPQ 351 (9165); *In re Sichert*, 196 USPQ 209, 212-213 (CCPA 1977). The evidentiary standard to be used when determining whether one skilled in the art would question the objective truth of Applicants' statement of utility or its scope is a preponderance of the totality of the evidence under consideration. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that Applicants' assertion enjoys, the Office must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' statement of utility. For the reasons explained below, Applicants respectfully maintain that the Office has not met this burden.

The Office action rejects the evidence (Pollack, Orntoft, Hyman, Bermont, Varis, and Hu) cited by Applicants, and instead contends that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility because the published literature in the field demonstrates that there is not a strong correlation between mRNA abundance and protein expression levels.

More specifically, the Office action rejects Applicants' reliance on the Pollack, Hyman, and Varis references because these references allegedly do not examine whether the observed correlation between gene amplification and mRNA overexpression also correlates with protein overexpression.

The Office action also rejects Applicants' reliance on the Bermont reference because, according to the Office, although Bermont teaches that gene amplification and overexpression correlate with protein overexpression, Bermont does not provide any *quantitative* data that could be used to determine what degree of gene overexpression results in higher protein levels.

Further, the Office action rejects the evidence presented in Orntoft. According to the Office action, Applicants' reliance on Orntoft is rejected because Orntoft examined only the most abundant proteins. Orntoft also is rejected because, according to the Office action, Orntoft does not examine correlation between gene amplification and protein overexpression for individual genes. Additionally, Orntoft is rejected because Orntoft concentrates on regions of chromosome with strong gains of chromosomal material while PRO347 was corrected for aneuploidy.

In a similar vein, the Office action rejects Applicants' reliance on Hu because according to the Office, Hu examines correlation of amplification of a known oncogene, MET (*which is more highly amplified than PRO347*), with overexpression of the encoded protein.

Applicants respectfully disagree that these are proper bases for rejecting Applicants' reliance on these references. First, even assuming *arguendo* that Pollack, Hyman, and Varis only teach correlation between gene amplification and mRNA levels, these references still do not establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility.

Second, even if Bermont fails to provide *quantitative* data, this reference still supports Applicants' assertion that gene amplification correlates with protein overexpression because it teaches that overexpression of the p185 protein, an indicator of breast cancer, is usually associated with amplification of the c-erbB-2 gene that encodes the p185 protein. Significantly, the lack of quantitative data in Bermont does not establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of Applicant's assertion of utility. Thus, the Office has not met its burden of overcoming the teachings of Bermont reference, which support Applicant's assertion of utility.

Third, Orntoft teaches correlation of gene amplification and protein overexpression in human bladder cancer. Indeed, Orntoft reports that for human bladder tumors, gene amplification in the bladder tumor tissues showed a "*striking correspondence*" to protein expression levels. Orntoft at 44 (emphasis added). Contrary to the statements in the

Office action, Orntoft does not teach that only the most abundant mRNAs correlate with a high level of protein expression. Rather, at the quoted language, Orntoft *et al.* explain that they examined the most abundant and well focused proteins because these were the only known proteins. Significantly, Orntoft examined whether there was correlation between gene amplification and protein overexpression for samples that showed at least a 2-fold change (increase or decrease) in DNA copy number and/or mRNA expression level. *See* Orntoft at Figure 1. Indeed, as shown in Table II of the Orntoft reference, 9 of the 11 proteins whose expression levels correlated with both mRNA and gene dose changes had transcription alteration levels ranging from 1.6 fold up to 5.7 fold up. The amount of gene amplification for PRO347 disclosed by Applicants is similar, approximately 2 to 5 fold. More specifically, Table 10, found at pages 125-126 of the present specification, discloses ΔCt values ranging from 1.0 to 2.645 for PRO347. One ΔCt is defined as corresponding to 1 PCR cycle or approximately a 2-fold amplification relative to normal. Thus, PRO347 amplification levels range from approximately 2.0 fold up to 5.29 fold up and clearly are within the range examined, *and shown to correlate with increased protein expression levels,* in the Orntoft reference.

Further, the teachings of Orntoft *i.e.,* that gene amplification correlates with protein overexpression, are not limited to instances where only aneuploidy is involved. Rather, Orntoft explains that "[i]n this investigation we have *combined* genome-wide technology for detecting genomic gains and losses (CGH) *with gene expression profiling techniques* (microarrays and proteomics) to determine the effect of gene copy number on transcript and protein levels in pairs of non-invasive and invasive human bladder TCCs." Orntoft at 37 (emphasis added). Thus, the correlation between gene copy number, mRNA transcript level, and protein expression level disclosed in Orntoft is not only directly applicable to, but also supports, Applicants' assertion of utility for the PRO347 polypeptide based on the disclosed amplification levels of the nucleic acid sequence encoding PRO347.

Hence, with regard to the Orntoft reference, the Office has not met its burden of establishing that in view of this reference, it is more likely than not that one of ordinary

skill in the art would doubt the truth of Applicants' assertion of utility. Therefore, the Office has not overcome Applicants' reliance on the Orntoft reference as support for the asserted utility of PRO347 polypeptides.

Fourth, although the Hu reference Applicants previously submitted for the Office's consideration (Hu et al., "Profiling of Differentially Expressed Cancer-related Genes in Espohageal Squamous Cell Carcinoma (ESCC) Using Human Cancer cDNA Arrays: Overexpression of Oncogene *Met* correlates with tumor differentiation in ESCC." 2001. *Clin. Cancer Research,* 7:3519-3525), focuses on a known oncogene, *Met,* this alone does not make it more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility. Indeed, Hu expressly teaches a positive correlation between gene amplification and protein overexpression for *Met* in cancerous tissues. Moreover, Hu references a related article wherein Hu reports the examination of the protein expression levels for four additional genes, previously found to be amplified in esophageal cancer. *See* Hu at page 3523, referring to results reported at Hu *et al.,* "Identification of Differentially Expressed Genes in Espohageal Squamous Cell Carcinoma (ESCC) by cDNA Expression Array: Overexpression of *Fra-1, Neogenin, Id-1,* and *CDC25B* Genes in ESCC." 2001. *Clin. Cancer Research,* 7:2213-2221 (attached hereto as Appendix 2 for the Examiner's convenience).

This second Hu reference reports that four genes first identified as being differentially expressed in ESCC compared with normal esophageal epithelium using a cDNA expression array hybridization assay were selected for further study of their protein expression levels. In particular, this second Hu reference reports that the protein products of these four genes, *Fra-1, Neogenin, ID-1,* and *CDC25B,* "were found to be overexpressed in both the ESCC cell lines and their corresponding primary tumors . . . [thereby] validating the cDNA array results." Hu at 2216.

Thus, the two Hu *et al.* references teach 100% correlation between gene amplification and protein over expression for five different nucleic acid sequences. Applicants respectfully submit that in view of the teachings of both Hu references, one of ordinary skill in the art would not doubt Applicants' assertion of utility. Rather, the teachings of

Hu *et al.* clearly support Applicants' assertion of utility. Applicants maintain that the Office has not met its burden of establishing that it is more likely than not that, in view of the teachings of Hu, one of ordinary skill in the art would question Applicants' assertion of utility.

Furthermore, as previously argued, the Haynes and Gygi references cited in the Office action do not outweigh the teachings of the above-discussed references, which are relied on by Applicants. As an initial matter, neither Haynes nor Gygi examine expression levels in human cancerous tissues. Rather, these references generically examine whether gene amplification in yeast correlates with protein overexpression. PRO347 was isolated from human lung and colon tumor tissues and therefore the teachings of the references cited by Applicants (Pollack, Hyman, Varis, Bermont, Orntoft, and Hu), which examine whether there is a correlation between gene amplification and protein overexpression in human cancerous tissues are more relevant and outweigh the teachings of Haynes and Gygi.

Additionally, although the Chen reference cited in the Office action examines correlation between gene amplification and protein overexpression in human lung adenocarcinomas, the teachings of Chen by themselves do not make it more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility.

This is particularly true when the Chen reference is considered with the totality of the evidence, as it must be. Indeed, although Chen "*suggests* that it is not possible to predict *overall* protein expression levels based on *average* mRNA abundance in lung cancer samples," Chen does disclose that in 17% of the samples examined, there was a positive correlation between mRNA abundance and protein overexpression. Chen at 311-12 (emphasis added). Additionally, Orntoft teaches that gene amplification levels very similar to those disclosed in the present specification in connection with PRO347 show a "striking correspondence" to protein overexpression levels. Even further, the two Hu references discussed above teach that 100% (5/5) of the genes examined displayed differential expression patterns in human cancerous tissue versus non-

cancerous tissue, and that the differential gene expression in the cancerous tissues correlated to elevated protein expression in those tissues. Bermont provides even further evidence, in a cancerous human system, that protein overexpression correlates with gene amplification. Thus, based on the *totality* of the evidence, one of ordinary skill in the art would believe it to be more likely than not that the PRO347 polypeptide is overexpressed in lung and colon cancer tissues. Indeed, the Office has not satisfied its burden of establishing that it is more likely than not that one of ordinary skill in the art would doubt the truth of Applicants' assertion of utility for the claimed polypeptide.

Significantly, a 35 U.S.C. § 101 rejection should only be sustained where the asserted utility violates a scientific principle or is *wholly* inconsistent with contemporary knowledge in the art. *In re Gazave,* 379 F.2d 973, 978 (CCPA 1967). The Office action rejects Applicants' reliance on *In re Gazave* on the basis that the *Gazave* case is factually distinguishable. In particular, the Office argues *In re Gazave* does not apply in this case because the present specification does not set forth explicit evidence that the PRO347 polypeptide is overexpressed in lung and colon cancer tissue, and no subsequent data has been provided. Applicants respectfully disagree that this is a proper basis for rejecting application of the holding of *In re Gazave* to the present case. In particular, the holding of *In re Gazave* should apply regardless of whether similar evidence is presented in this case as was presented in that case. Rather than compare the types of evidence at issue in the cases, *In re Gazave* requires the Office to consider whether the *totality of the evidence* submitted regarding the asserted utility demonstrates that the asserted utility violates a scientific principle or is *wholly* inconsistent with contemporary knowledge in the art. For the reasons discussed above, Applicants respectfully maintain that the *totality* of the evidence does not demonstrate that the asserted utility violates a scientific principle, nor is the *totality* of the evidence *wholly* inconsistent with contemporary knowledge in the art.

For all these reasons, Applicants maintain that this rejection is improper and should be withdrawn.

35 U.S.C. § 112 ¶ 1, Enablement-Utility

Claims 25-34 stand rejected under 35 U.S.C. § 112 ¶1, because it is alleged that the presently claimed invention is not supported by either a specific asserted utility or a well established utility, and therefore, one skilled in the art would not know how to use the claimed invention. As discussed in the remarks above, addressing the rejection under 35 U.S.C. § 101 for lack of utility, Applicants respectfully submit that the claimed polypeptide is supported by a specific, substantial, and credible utility. Thus, Applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

35 U.S.C. § 112 ¶ 1, Written Description

Claims 25-26, 33, and 34 stand rejected under 35 U.S.C. § 112 ¶ 1, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skill in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants have herein canceled claims 25 and 26 without disclaimer or prejudice to pursuing the invention of claims 25 and 26 in a continuing application. Applicants have amended claim 33 herein such that it no longer depends from canceled claim 25 but now depends from pending claim 27. Claim 34 depends from claim 33. Therefore, Applicants have overcome this ground of rejection and respectfully request that it be withdrawn.

SUMMARY

Applicants believe that currently pending Claims 27-34 are patentable. The Examiner is invited to contact the undersigned attorney for Applicants via telephone if such communication would expedite allowance of this application.

Respectfully submitted,

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